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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,317	LEENDERS ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Applicant's reply received 7/15/08. Claims 1-10 are pending. Claims 8 and 9 are withdrawn. No claims are cancelled. Claims 1-7 have been amended. No claims are new.

Response to Objection to the Specification

The objections to the specification are withdrawn with the Applicant's addition of a Brief Description of Drawings that has been added to page 3.

Response to Applicant's Arguments— 35 U.S.C § 112

In the response submitted by the Applicant the 35 U.S.C § 112 rejection of claims 1-7 and 10 is withdrawn in light of the Applicant's amendment.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-5, 7 and 10 over Leskovar et al. were considered but not found persuasive. The Applicant argues that the limitation of a composition "consisting essentially of" the components of claim 1 is not taught by Leskovar et al. As mentioned in the previous Office Action (mailed 3/17/08) and repeated here, the direction provided to the Examiner by M.P.E.P. § 2111.03 is as follows:

> "The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA

> 1976) (emphasis in original)" and "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355" [Emphasis Added]

The Examiner did not find any indication in the specification or claims what the novel and basic characteristics actually are. Furthermore in the Applicant's response the Examiner was not directed to "what the basic and novel characteristics actually are". As mentioned in the previous Office Action, until such evidence is pointed out to the Examiner, claim 1 will remained interpreted by the Examiner as "consisting of" rather than "consisting essentially of".

The Applicant argues that the language of claim 1 excludes the use of conjugated anthracyclines. While it is true that the term "anthracylines" is part of a Markush group this does not in itself exclude anthracyclines that are conjugated to an antibody. Indeed anthracyclines is a plural term that while including those molecules such as doxorubicin and epirubicin listed by the Applicant on page 8 of their response, it does not exclude that these compounds are not conjugated to an antibody. Indeed Leskovar et al. specifically teach that the anthracycline, doxorubicin, even after being conjugated to an antibody is still useful to treat tumors (Leskovar, paragraph 140). Therefore one of ordinary skill in the art would recognize that not only is the activity of the anthracycline intact even after conjugation to the antibody but that these compounds would still fall under the classification of an

"anthracycline" since they still share a similar structure which is responsible for their tumor fighting activity.

The Applicant argues that the combination of claim 1 has unexpected or synergistic results for cancer therapy. The Applicant attributes these results to the "assumed mechanism" (Applicant's response, page 9, 1st full paragraph) having glutaminase activity. However the rejection of this by the Examiner was not based on the general mechanism, but on the nexus between the claims and the showing of unexpected results. Provided that "cancer" is a disease that involves multiple cell types and can require a wide range of treatments to be effective, it is not obvious to one of ordinary skill in the art that the treatment for a particular kind of cancer will necessarily work on all types. The same is true in this instance where the proposed synergistic results by the Applicant cannot be assumed to be synergistic for all forms of cancer. Indeed the Applicant's data in figures 1-5 supports this where specific treatments of glutaminase, anthracyclin or cis-platinum complexes alone do not have the same effect on all the cell types tested and clearly certain treatments are far more effective on some cell types as opposed to others. Therefore the nexus between the synergism proposed by the Applicant for the broad classes of compounds with glutaminase activity and antineoplastic agents against the broad genus of cancer and the evidence provided is not present.

The Applicant argues that glutaminase enzymes conjugated to the antibodies as taught by Leskovar et al. do not necessarily have glutaminase activity. This argument is merely the argument of counsel and is unsupported by evidence or declarations of

those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The Applicant argues that Leskovar et al. does not teach using both anthracyclines and glutaminase in the same compositions. This was addressed by the Examiner in the previous Office Action on page 6, first full paragraph. Furthermore Leskovar et al. teaches that both the glutaminase conjugate and the anthracycline conjugate are useful to treat tumors (paragraph 192, 23 and 140). M.P.E.P. § 2144.06 states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Therefore it is *prima facie* obvious to one of ordinary skill in the art to combine the glutaminase conjugate with the anthracycline conjugate into the same composition since Leskovar et al. teach they are used for the same purpose. Therefore the rejection stands and is repeated below.

Claims 1-5, 7 and claim 10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403). This reference is written in German. However it has a U.S. Patent Publication (US 2002/0094542) which is a 371 and as such is an English language equivalent document (see M.P.E.P., Appendix L, 35 U.S.C. 371 National stage: Commencement.) The Examiner will cite the U.S. Patent Publication for convenience, but the rejection remains over WO 89/09620.

These claims are to a combined pharmaceutical preparation comprising as active substances: (a) at least one compound having glutaminase activity (**GA**) and (b) at least one antineoplastic agent selected from platinum complexes and anthracyclines. Claim 2 limits claim 1 by teaching the compound having GA is glutaminase, glutaminase-asparaginase, glutaminase analog, derivative or modification of the same and is either of natural origin or is produced synthetically. Claim 3 limits that the compound with GA is from Pseudomonas. Claim 4 limit that the GA compound is modified. Claim 5 limits the type of anthracycline. Claim 7 teach the pharmaceutical preparation further comprises a pharmaceutically acceptable carrier for oral or parenteral administration.

Leskovar et al. teach a pharmaceutical preparation that comprises the Component A which includes anthracyclines such as doxorubicin and daunomycin that have been modified by conjugating them with antibodies (paragraphs 21-23). Leskovar et al. also teach that their pharmaceutical preparation can comprise antibody immunoconjugates of the enzymes asparaginase and glutaminase (paragraph 192). Leskovar et al. does not specifically teach the addition of both the anthracyclines and glutaminase enzymes in the same composition. However Leskovar et al. does teach

that antibody conjugates of xenogeneic proteins can be admixed with Component A and either administered parenterally or orally and modified with PEG (polyethylene glycol) (paragraph 25-26). One of ordinary skill in the art would recognize that that a composition with active substances such as enzymes and anthracyclines would need to be mixed with a pharmaceutically acceptable carrier such as water to be administered parenterally or orally.

It would therefore have been obvious for the person of ordinary skill in the art to modify the invention of Leskovar et al. to combine an enzyme such as glutaminase with component A, which they teach as an anthracycline such as doxorubicin. Leskovar et al. provides express motivation and reasonable expectation of success by stating that "conjugates, composed of xenogeneous proteins...can be admixed to the component A" (paragraph 26).

Furthermore it would be obvious to combine the anthracycline and glutaminase since they are two components known for the same purpose (see M.P.E.P. § 2144.06). In this case the treatment of cancer (paragraph 140 and 192). This would apply to anthracyclines that are immunoconjugated or not, since the art is replete with references that unmodified anthracyclines alone are effective against the treatment of caner

While Leskovar et al. does teach the use of glutaminase and asparaginase (paragraph 192) they do not teach that the compound having glutaminase activity is *Pseudomonas* 7A glutaminase-asparaginase. However it would be obvious to one skilled in the art that any glutaminase regardless of its source will perform the same

chemical reaction and can therefore be used for the same purpose unless evidence to the contrary is provided (M.P.E.P. § 2144.06).

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the reference listed above and as such claims 1-5, 7 and claim 10 are not allowable.

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-7 over Leskovar et al. as applied to claim 1-5, 7 and 10 above in view of Housman et al. were considered but not found persuasive.

Concerning the remaining 35 U.S.C § 103 (a) rejections in the Office Action the Applicant argues that since the amendments of claim 1 overcome the teachings of Leskovar that they in turn overcome the remaining rejections that use this reference. However as detailed above the Examiner disagrees and believes that the combination of Lesokovar in view of Housman et al is proper and in the absence of arguments to the contrary these rejections stand for the amended claims and are repeated below.

Claim 1-7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leskovar et al. (WO 89/09620 of PCT/EP89/00403) as applied to claim 1-5, 7 and new claim 10 above, and further in view of Housman et al. (U.S. Patent # 6,200,754, 2001).

The details of clams 1-5, 7 and 10 and their rejection are described in the above 103(a) rejection over Leskovar et al.

Claim 6 limits the pharmaceutical preparation comprising cis-platinum, oxaliplatinim or/and carboplatinum.

While Leskovar et al. teach the use of other DNA crosslinking compounds such as mitomycin C (Leskovar et al. paragraph 23) in a composition for cancer treatment he does not teach the specific use of DNA crosslinking agent cis-platinum. However Housman et al. teach that mitomycin C and cis-platinum are both DNA crosslinking agents (col 22, lines 14-15) and one of ordinary skill in the art would recognize them as common drugs for cancer treatment (col 21, line 55 to col 22, line 20). Therefore it would be obvious to replace cis-platinum or other DNA crosslinking agents such as oxaliplatinum and carboplatinum since these are art-recognized equivalents for the same purpose (M.P.E.P. § 2144.06).

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-7 and 10 are not allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
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/Leon B Lankford/
Primary Examiner, Art Unit 1651